Initial antimicrobial use in a medical adult intensive care unit: indication and cost analysis at Steve Biko Academic hospital, Pretoria

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DECLARATION

I, Regina Bester, declare that the dissertation hereby submitted to the Sefako Makgatho Health Sciences University, for the degree of Master of Science (Medical) in Pharmacy, in the Faculty of Health Sciences, School of Health Care Sciences, has not previously been submitted by me for a degree at this or any other University; that it is my work in design and execution, and that all material contained herein has been duly acknowledged.

______________________________  __________________
Bester, R (Mrs)                      Date
DEDICATION

The work of this clinical study is dedicated to my God, my husband Cobus, my son Nicolaas and my parents. Thank you for your support, without it I would never have succeeded.
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I would like to thank the following people for their support and hard work during the course of this study. Without each and every one, this study would not have been possible.

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ABSTRACT

Background: Antimicrobial resistance is increasing throughout the world. In hospitals an estimated of 50% of antimicrobial usage is unnecessary or inappropriate\textsuperscript{1,2}. The study intended to investigate the use of initially prescribed antimicrobial agents in an adult intensive care unit at Steve Biko Academic hospital.

Method: All patients that were initiated on antibiotics during this study period were included in the study. The study was done over 7 months and 52 patients’ data were collected.

The objectives of the study were as follows:
- To identify initially prescribed antimicrobials
- To determine if antimicrobials are prescribed appropriately according to a patient’s diagnosis, weight, renal markers, hepatic markers, infection biomarkers, considering indication, dose and duration of treatment.
- To determine the direct costs associated with the initially prescribed antimicrobial therapy.

Results: 52 patients were included in the study. The mean length of hospital stay (LOS) in the MICU for all patients was 10.63 days (range 3 to 23 days). During the study infection biomarkers were used to assist with the decision to start and to stop antibiotics. 60% of antibiotics were prescribed appropriately and 40% antibiotics were prescribed inappropriately. During the study, 76 antibiotics were prescribed for the 52 patients. The top three initially prescribed antibiotics during the study period were meropenem, piperacillin/tazobactam and clarithromycin. During the study the most positive cultures that were taken were blood cultures. The total treatment cost for all initially prescribed antibiotics was R209 140.40.

Conclusion: Meropenem was the antibiotic that was prescribed the most during the study period, with a total treatment cost for all initially prescribed antibiotics of R209 140.40. The majority of antibiotics were prescribed appropriately according to infectious biomarkers and was compared to standard treatment guidelines and essential drug list for adults at hospital level.
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LIST OF ABBREVIATIONS

ASP – Antimicrobial Stewardship Programme
LOS - Length of stay
SBAH – Steve Biko Academic Hospital
VAP - Ventilator Associated Pneumonia
HAP - Hospital Acquired Pneumonia
MICU - Medical Intensive Care Unit
ICU - Intensive Care Unit
WBC - White Blood Cell
CRP - C-reactive protein
PCT - Procalcitonin
IV - Intravenous
PO - Oral
IDSA – Infectious Disease Society of America
PIDS - Paediatric Infectious Disease Society
SIRS – Systemic Inflammatory Response Syndrome
COPD - Chronic Obstruction Pulmonary Disease
IPD - Invasive Pneumococcal Diseases
NHLS - National Health Laboratory System
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CHAPTER 1

INTRODUCTION

1.1 Introduction

This introductory chapter describes the background and rationale for this study. The primary and secondary research questions are provided; followed by the aim and objectives to be accomplished. The importance of conducting this study is described. An outline of the chapters of the dissertation concludes this chapter.

1.2 Problem statement and rationale for the study

Antimicrobial resistance is increasing throughout the world. In hospitals an estimation was done that 50% of antimicrobial usage is either unnecessary or inappropriate (Doron and Davidson, 2011; Martin, Goff, Karem, Dombrowski and Dechant, 2009): The timely selection and administration of appropriate antimicrobial therapy can significantly impact treatment outcomes, especially in patients with severe or life-threatening infections (Drew, 2009). Antimicrobial stewardship is a coordinated effort to ensure the judicious and effective use of antimicrobial therapy that includes, but is not limited to, the appropriate selection, dosing, route of administration, and duration of antimicrobial therapy (Martin et al, 2009). The goal of the antimicrobial stewardship programme (ASP) is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use and reduction in health care costs without adversely affecting the quality of care (Martin et al 2009).

At Steve Biko Academic Hospital (SBAH) a need for an ASP was identified by the Head of Infectious Diseases, Professor A Stoltz (2012). The study intended to investigate the use of initially prescribed antimicrobial agents in an adult intensive care unit at Steve Biko Academic hospital (SBAH) as part of an antimicrobial stewardship roll out programme. Initially prescribed antibiotics are extremely important in high risk patients. (e.g. ventilator associated pneumonia (VAP), septic shock etc.) There can be an average decrease in survival of 7.6% for every hour of delay in antibiotic administration. For every ten minutes a survival is decreased by 1% (Pong and Bradley, 2005). Thus guidelines recommend prompt antimicrobial

For the purposes of this study initially prescribed antibiotics are defined as all antibiotics initiated in the medical intensive care unit (MICU). This study aimed to explore factors surrounding initially prescribed antibiotics in a MICU, and the direct medicine related costs at SBAH.

1.3 Research questions
Were initially prescribed antimicrobials appropriately used according to the patient’s clinical parameters, considering indication, dose and duration in the MICU at Steve Biko Academic Hospital?

What is the cost of initial antimicrobial use considering clinical biomarkers in the MICU?

1.4 Aim of the study
The aim of the study was to investigate the initial use of antimicrobials as prescribed in a medical adult intensive care unit at Steve Biko Academic Hospital part of an antimicrobial stewardship roll out programme focusing on:

- Indication
- Duration of use
- Cost, and
- Clinical biomarkers
1.5 Objectives of the study

The objectives of the study were as follows:

- To identify initially prescribed antimicrobials for a MICU.
- To determine if antimicrobials were prescribed appropriately according to patient diagnosis, weight, renal (urea and creatinine, creatinine clearance using Cockcroft and Gault equation) and hepatic markers (ALT, AST, GGT, Alk Phos, LDH, Total Bili and Direct Bili) as compared to the Standard Treatment Guidelines and Essential Medicine List for Adults at Hospital Level of 2008.
- To investigate the use of antimicrobials against infection biomarkers (WBC count, CRP, temperature, blood culture, procalcitonin) considering indication, dose and duration of treatment and compared to the Standard Treatment Guidelines and Essential Drug List for Adults at Hospital Level.
- To determine the direct costs associated with the initially prescribed antimicrobial therapy for a patient in a MICU unit using daily defined dose.

1.6 Importance of the study

Antibiotic resistance is one of the world’s most pressing health threats. The way in which antimicrobials are used today (and even more specifically in one patient) directly impact their effectiveness tomorrow, they are a shared resource! Antimicrobial overuse and misuse increases the development of drug resistant organisms. Resistant organisms are able to withstand attacks by antimicrobial medicines rendering standard treatment ineffective (Dellit, Owens, McGowan, Gerding, Weinstein, Burke, Huskins, Paterson, Fishman, Carpenter, Brennan, Billeter, Hooton, 2007).

Antimicrobial resistance is increasing; however, antimicrobial drug development is slow. Now, more than ever, antimicrobial stewardship is of the utmost importance as a way to optimize the use of antimicrobials, prevent the development of resistance and improve patient outcomes (Martin et al, 2009).
1.7 Outline of the study

Chapter 1 introduces the reader to the study and this includes the background and the rationale for the study. The aim and objectives of the study are laid out thereafter. Chapter 2 includes the literature review and studies that have been conducted that will help with the research question concerning this study. Chapter 3 provides a step-by-step and detailed description of the methodology of the study. Chapter 4 contains the results and discussion of the study. Chapter 5 is a summary of the results.
CHAPTER 2

LITERATURE REVIEW

This chapter presents the literature review on the topic under study, and has been sub-divided into sections. The chapter starts with Section 2.1 which is an introduction on antimicrobial stewardship. This is followed by Section 2.2 an outline of antimicrobial stewardship and cost, Section 2.3 antimicrobial use in the intensive care unit and Section 2.4 a detailed discussion of infectious diseases biomarkers.

2.1 Antimicrobial stewardship – An introduction

Antimicrobial stewardship has been defined as “the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance (Koeni and Truwit, 2006).” The goal of antimicrobial stewardship is three-fold (Doron and Davidson, 2011):

The first goal is to work with health care practitioners to ensure each patient receives the most appropriate antimicrobial with the correct dose and duration (Doron and Davidson, 2011)

The second goal is to prevent antimicrobial overuse, misuse, and abuse. In both the hospital and the outpatient setting, physicians use antibiotics unnecessarily (Doron and Davidson, 2011)
The **third goal** is to minimize the development of resistance. At both the individual patient level and at the community level, antibiotic use changes susceptibility patterns (Doron and Davidson, 2011)

The appropriate use of antimicrobials has the potential to improve efficacy, reduce treatment-related costs, minimize drug-related adverse events, and limit the potential for emergence of antimicrobial resistance (Drew, 2009).

An ASP was fully implemented at the University of Maryland Medical Center in July 2001 (beginning of fiscal year [FY] 2002). The programme continued for seven years. A descriptive cost analysis was done before, during, and after the programme. There was a health care cost reduction of approximately $3 million within the first 3 years (Standiford, Chan, Tripoli, Weekes and Forrest, 2012).

During the same study, (Standiford et al, 2012) the duties of the antibiotic stewardship team were to provide an active computer-assisted real-time review of antimicrobial orders for the designated restricted antimicrobials and to provide active interventions when necessary. During their review, the team attempted to (a) identify ineffective or excessive antimicrobial coverage, (b) assure that the orders adhered to policies and guidelines, (c) discontinue unnecessary double coverage, (d) determine patients whose treatment could be converted safely from parenteral to oral therapy (IV-PO), and (e) suggest infectious diseases consults for difficult and complex cases. The team’s priorities for review were those patients receiving restricted antimicrobial agents.

Up to 50% of antimicrobial use in all hospitals is unnecessary or inappropriate. Inadequate infection prevention and -control measures and the transmission of community acquired infections caused by resistant pathogens contribute to the problem of antibiotic-resistant infections in hospitals. Antimicrobial resistance is associated with increased mortality, prolonged hospital lengths of stay, and increased health care costs (Martin et al, 2009).
Two proactive strategies for promoting antimicrobial stewardship include: (a) formulary restriction and pre-authorization and (b) prospective audit with intervention and feedback. Other supplemental strategies involve education, guidelines and clinical pathways, antimicrobial order forms, de-escalation of therapy, intravenous-to-oral (IV-to-PO) switch therapy and dose optimization (Drew, 2009).

Formulary restriction and preauthorization involves limiting the use of an antimicrobial agent to certain indications, prescribers, physician services, or patient populations, often depending on local antimicrobial resistance patterns and patient safety issues. Immediate and substantial reductions in antimicrobial use and costs can be achieved through these strategies, although increases in the use of and resistance to an alternative antimicrobial agent may result (Martin et al, 2009).

As Sir Alexander Fleming predicted in his Nobel Lecture, antimicrobials – since their introduction – have been pivotal in the prevention and treatment of infections (Ojeniran, Shouval, Miskin, Moses and Shmueli, 2010). However, the increasing use of antimicrobials has led to a situation of appropriate and inappropriate use. Although there is no consensus on the definition of 'appropriate' therapy,"…appropriate antimicrobial therapy implies that the indication, choice of drug, timing of administration, route, dosage, frequency and duration of administration have been rigorously determined". Allowance should also be made for switching broad empiric therapy to a narrower definitive treatment and from intravenous to oral drugs (Ojeniran, 2010).

### 2.2 Antimicrobial stewardship and cost

Appropriate antibiotic use is of both clinical and economic significance to any health system and should be given adequate attention (Ojeniran, 2010).
According to Drew (2009) an ASP has the potential to reduce antimicrobial costs by limiting the overuse and inappropriate use of these agents and by promoting active intravenous-to-oral (IV-to-PO) switch therapy. By reducing the unnecessary use of antimicrobials, a well-designed ASP has the additional advantages of reducing (a) the risk of drug-related adverse events and their associated costs, and (b) the emergence of resistance and, hence, minimizing infections caused by resistant pathogens.

Furthermore Drew (2009) states infections caused by resistant organisms are associated with poorer clinical outcomes, prolonged hospital length of stay (LOS), and higher overall costs compared to infections caused by susceptible organisms. Therefore, by promoting the appropriate use of antimicrobials, ASPs can have a broad impact on improving clinical outcomes while reducing overall health care costs.

Resistance to antibiotics results in an extensive increase in costs to the patient, family, hospital, and society, due to the need for the use of more expensive drugs for second line treatment, more tests and much longer stays in hospital, as well as longer sick-leave, or even premature death (ANON, 2008).

A study done in 2013 on invasive pneumococcal diseases (IPD) stated that the clinical disease burden of IPD increased significantly with age and direct medical costs from IPD were substantial, regardless of age and co-morbid conditions. (Song, JY, Choi JY, Lee JS, Bae I, Kim YK, Sohn JW, Jo YM, Choi WS, Lee J, Park KH, Kim WJ and Cheong HJ, 2013)

One reason antimicrobial-drug resistance is of concern is its economic impact on physicians, patients health-care administrators, pharmaceutical producers, and the public. (McGowan JE, 2001).
The economic cost of antimicrobial-drug resistance for health-care businesses is in the measures they must take to preserve the effectiveness of antimicrobial agents in the care group. These measures may include costs for a series of different drugs and services, as well as for personnel time, supplies, space, and equipment for institutional programs to deal with antimicrobial-drug resistance (e.g., pharmacy and therapeutics committees, antimicrobial-drug use review, practice guidelines). The benefit is decreased costs associated with care of patients infected with resistant organisms. (McGowan JE, 2001).

Costs for laboratory tests, radiologic studies, bronchoscopies, or other diagnostic procedures are part of diagnostic costs and primarily of concern to the health-care institution when these costs cannot be passed on to the patient or an insurer. The same is true of costs for purchase and administration of antimicrobial drugs and other therapeutic agents. Patients experience both direct costs of health care and indirect costs (e.g., loss of productivity resulting in reduction in income). Other types of indirect costs of antimicrobial-drug resistance are costs to the drug industry resulting from diminishing marketability of their drugs and costs to businesses for loss of workers’ productive time. All these factors are part of the economic impact of resistance. (McGowan JE, 2001).

An article that was published in 2012, by Standiford et al. stated that cost savings after the programme was implemented were observed in all 3 major areas of the medical centre: the cancer centre, the shock trauma centre, and the main hospital. However, the savings that occurred during the first 3 years of implementation were most apparent in the cancer centre (∼$2,000,000). Cost savings also occurred in the medical intensive care unit (MICU), the surgical ICU (SICU), and the transplantation service.

In 2009, the level of support for the ASP from administrators was higher at university hospitals than community hospitals (Martin et al, 2009). Most respondents with established ASP indicated that new data were needed to convince administrators to continue to support the ASP and influence clinicians to adhere to ASP recommendations. Data demonstrating cost savings from the ASP was considered
most useful to administrators. Clinicians sought data demonstrating a reduction in antimicrobial resistance (Martin et al, 2009).

Pharmacists can play an important role in reducing the threat to public health and costs of hospital-acquired antibiotic-resistant infections through antimicrobial stewardship (Martin et al, 2009).

In a prospective study of antibiotics cost containment in a university teaching hospital over a 13 year period, changes were documented, and the clinical pharmacist calculated the monthly savings from the antibiotic changes. Cost savings were determined by calculating the daily cost for the difference between the antibiotic originally prescribed and the newly recommended one, multiplied by the estimated duration of additional therapy for a specific indication. The duration of treatment was based on published guidelines, expert opinions, and local consensus for each infectious disease monitored. The clinical pharmacist collected monthly data to determine the total savings, the number of changed antibiotics, the number of doses before the antibiotic change, and the monthly cumulative savings (Kuyumjian, Levine, Gross, and Lo Presti, 2002).

Overall, ASP has been shown to be cost-effective. It has the added benefit of determining the costs associated with the infectious disease diagnosis of interest. Costs may include, not only the price of the antimicrobials but also those associated with laboratory tests and with adverse events from using the incorrect dose or type of antimicrobial (Doron and Davidson, 2011)

### 2.3 Antimicrobial use in the intensive care unit

The implementation of an ASP can present a challenge because of limited resources and other barriers. Institutional needs and available resources should be taken into consideration in planning a strategy for ASP implementation. It should optimize the
use of limited resources, overcome barriers to implementation, and improve clinical outcomes (Martin et al, 2009).

The primary goal of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms (such as Clostridium difficile), and the emergence of resistance (Delit et al, 2007) A secondary goal of antimicrobial stewardship is to reduce health care costs without adversely impacting quality of care (Dellit et al, 2007).

According to Dellit, et al, (2007) a review by a pharmacist and an infectious diseases physician of 625 patients receiving combination antimicrobial therapy led to streamlining recommendations in 54% of antimicrobial courses over 7 months, resulting in a projected annual saving of $107,637. Optimization of antimicrobial dosing based on individual patient characteristics, causative organism, site of infection, and pharmacokinetic and pharmacodynamic characteristics of the drug is an important part of antimicrobial stewardship.

In the absence of risk factors for multidrug-resistant bacteria, the clinician should choose empirical therapy for Streptococcus pneumoniae, Haemophilus influenzae, methicillin-sensitive Staphylococcus aureus, and antibiotic-sensitive gram-negative enteric organisms. Antibiotic choices include ceftriaxone, quinolones (levofloxacin, moxifloxacin, or ciprofloxacin), ampicillin/sulbactam, or ertapenem. When risk factors for multidrug resistant organisms are present, the clinician should consider not only the organisms listed above but also Pseudomonas aeruginosa, Klebsiella, Enterobacter, Serratia, Acinetobacter, Stenotrophomonas maltophilia, Burkholderia cepacia, and methicillin-resistant Staphylococcus aureus. Empirical therapy is broadened to include (i) either an antipseudomonal cephalosporin (cefepime or ceftazadime), anti- pseudomonal carbopenem (imipenem or meropenem), or a β-lactam/β-lactamase inhibitor (pipercacillin-tazobactam) plus (ii) an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or an aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin (Koeni and Truwit, 2006)
Antimicrobial use in the intensive care unit (ICU) is seemingly ubiquitous. An international, prospective, point prevalence study of more than 1200 ICUs documented that 71% of ICU patients received antimicrobials (Katsios, Burry, Nelson, Jivray, Lapinsky, Wax, Christian, Mehta, Bell and Morris, 2012)

This widespread use may be inappropriate, with recent studies estimating as many as 30% of regimens as unnecessary (Katsios et al, 2012). The consequences of unnecessary antimicrobial use (antimicrobial resistance, adverse events, and cost) necessitate judicious use (Katsios et al, 2012).

ASP represents organizational approaches to harmonize competing concerns of adequate antimicrobial coverage, adverse events and resistance and are well suited to ICU setting. A position statement from the Infectious Disease Society of America (IDSA) the Society for Healthcare Epidemiology of America (SHEA) and the Paediatric Infectious Disease Society (PIDS), deemed stewardship a “fiduciary responsibility for all healthcare institutions” and recommended mandatory implementation (Katsios et al, 2012)

In critically ill patients, one study documents up to 50% of positive cultures may actually represent contamination (Katsios et al, 2012). Positive microbial cultures in critically ill patients often prompt reflexive antimicrobial therapy, regardless of the sampling site or the contamination potential (Katsios et al, 2012).

Specifically, positive “sterile site” cultures (such as blood cultures) better represent true infection than positive “non-sterile site” cultures (such as wound and sputum cultures). Non-sterile sites are more likely to reflect colonization or contamination (Katsios et al, 2012).
Appropriate antimicrobial use should preferentially treat positive cultures from sterile sites rather than from non-sterile sites. Distinguishing between contamination and true positives can be difficult and clinicians may benefit from ASP assistance with regimen choice and education surrounding contamination potential (Katsios et al, 2012).

Although the literature suggests that ASPs are associated with reduced ICU antimicrobial utilization, how these results are achieved on an individual patient level is unclear (Katsios et al, 2012).

Although early institution of adequate antimicrobial therapy is lifesaving in sepsis patients, optimal antimicrobial strategy has not been established. (Diaz-Martin, Martinez-Gonzalez, Ferrer, Lwyba, Piacentini, Lopez-Pueyo, Martin-Loeches, Levy, Artigas and Garnadho-Montero, 2012)

Sepsis is a prevalent disorder and one of the main causes of death among hospitalized patients. Sepsis present at ICU admission and ICU-acquired sepsis clearly differ in the types of patients affected, the sources of infection, the microorganisms responsible, and the prognosis (Diaz-Martin, 2012).

Diverse studies have confirmed that the prompt institution of antimicrobial therapy against the causative pathogen is lifesaving in patients with severe sepsis. Although antibiotic therapy is the cornerstone in the treatment of sepsis, the optimal antimicrobial strategy has not been defined (Diaz-Martin, 2012).

Appropriate empiric antimicrobial therapy is crucial for the survival of a septic patient. Formerly, multidrug resistant pathogens were found almost exclusively in nosocomial infections. However, community-acquired infections are now often caused by antibiotic-resistant bacteria (for example, extended-spectrum b-lactamase producing *Enterobacteriaceae*, multidrug-resistant *Pseudomonas aeruginosa*, or methicillin-resistant *Staphylococcus aureus*) (Diaz-Martin, 2012).
This striking change in epidemiology may explain why the initial therapy frequently includes a combination of different antimicrobial agents (Diaz-Martin, 2012).

β-lactams, including carbapenems, are the most commonly used antibiotics in the critical care setting. Likewise, this antibiotic family constitutes the mainstay of empiric treatment in patients with severe sepsis or septic shock, whether administered alone or in combination with other antimicrobials. Carbapenems are more frequently prescribed in patients with nosocomial sepsis, although it is worth mentioning that one in five patients with community-acquired sepsis is treated empirically with a carbapenem (Diaz-Martin, 2012). This may reflect the increase in multidrug-resistant gram-negative pathogens in the community and carbapenems might have been analysed in conjunction with the rest of β-lactams. However, it was decided to analyse them separately from other β-lactams because of the broader-spectrum, major role in empiric antibiotic therapy and the widespread use in the ICU (Diaz-Martin, 2012).

Quinolones are used mainly in community-acquired infections and in combination therapy. The extended use of quinolones in combination therapy in patients with severe community-acquired pneumonia may explain the increasing rate of quinolone resistance among nosocomial gram-negative pathogens (Diaz-Martin, 2012).

The choice of empiric antimicrobial therapy is based on the clinical presentation of the infection, the characteristics of the patient, the local ecology and previous antibiotic exposure. Reducing the antibiotic pressure and side effects are the main reasons for choosing monotherapy. Conversely, the main reason for prescribing combination therapy for critically ill sepsis patient is to broaden the antimicrobial spectrum in an attempt to ensure the coverage of all likely pathogens (Diaz-Martin, 2012).

### 2.4 Infectious diseases biomarkers

Biomarkers for bacterial infection and sepsis, such as procalcitonin (PCT), have been used to shorten antimicrobial therapy without adversely affecting clinical
outcomes (Martin et al, 2009). Optimization of antimicrobial dosing based on individual patient characteristics, causative organism, site of infection, and pharmacokinetic and pharmacodynamic characteristics of the drug is an important part of antimicrobial stewardship (Dellit et al, 2007).

Over the past two decades PCT has been extensively studied as a serum marker of systemic infection and sepsis. Being the precursor of the active hormone calcitonin, PCT is a 116 amino-acid peptide that can be elevated by several orders of magnitude in systemic inflammation accompanying sepsis (Assink-de Jong, de Lange, van Oers, Nijsten, Twisk and Beishuizen, 2013) It has been shown that after trauma or surgery the levels of PCT usually stay below 1 ng/ml. On the other hand, PCT levels that are clearly above 1 ng/ml are often associated with severe bacterial infections that manifest themselves as sepsis and septic shock (Assink-de Jong et al, 2013)

Previous studies have shown that PCT-guided therapy is not only beneficial for respiratory tract infections, but also provide useful guidance for antimicrobial treatment in critically ill patients in the ICU who are treated for suspected bacterial infection (Assink-de Jong et al, 2013)

Clinical improvement defined as improvement of respiratory parameters, decreasing CRP, decreasing WBC and/or radiological signs of improvement were documented by laboratory results, radiology or clinical/nursing documentation, and respiratory parameters in mechanically ventilated patients (Wilke, Grube and Bodmann, 2011).

In the context of worldwide increasing antimicrobial resistance, good antimicrobial prescribing is now needed more than ever; unfortunately, information available to clinicians are often insufficient to rely on. Biomarkers might provide help for decision-making and improve antibiotic management (Dupuy, Philippart, Péan, Lasocki, Charles, Chalumeau, Claessens, Quenot, Guen, Ruiz, Luyt, Roche, Stahl, Bedos, Pugin, Gauzit, Misset and Brun-Buisson, 2013)
According to Dupuy et al, (2013) the principal objective of antibiotic prescribing is to ensure appropriate therapy when needed, while avoiding unnecessary or unduly prolonged therapy. Within this framework, obtaining adequate microbiological information is of paramount importance; unfortunately, such information is lacking in more than 50% of clinical situations where antibiotic therapy is prescribed, even in hospitalized patients.

Whereas clinical information is usually sufficient to initiate empiric therapy, they lack accuracy to tailor subsequent therapy and decide on its duration. Physicians’ decisions would be strengthened if they could get help from results of accurate biomarkers reflecting the diagnosis or evolution of the infectious processes. The field of infection-associated biomarkers has grown rapidly within the past few years and is still expanding; few of them, however, have gone through the hurdles of rigorous testing in the clinical arena to allow specifying their role in clinical practice (Dupuy et al, 2013)

Biomarkers from the host can be anatomical, physiological, biochemical (either circulating or membrane-bound), or molecular markers. The latter two categories are detected within a tissue or biological fluid (e.g., blood, cerebrospinal fluid, or urine) and their presence or absence, or over- vs. under-expression is the judgment criteria. Of note, more than 90% currently available biomarkers are used only within research program and have not been introduced within the field of clinical biology (Dupuy et al, 2013)

Currently accepted definitions for biomarkers have emerged from an expert panel driven by the U.S. National Institute of Health (NIH) and from regulatory definitions issued by the European Medicines Agency. (Dupuy et al, 2013)

A biomarker is “a biological characteristic, objectively measured (i.e., with acceptable accuracy and reproducibility) and used as an indicator for a physiological or pathological process, or of the activity of a medicine.” According to the NIH panel biomarkers can be stratified in two categories: prognostic markers, allowing to stratify patients according to their individual risk of having a specified outcome,
independently of therapy (or of the lack of therapy), and predictive markers, which allow to predict the potential benefit (efficacy) and/or the risks (toxicity) of a therapy according to the biomarker status (absent/present) (Dupuy et al, 2013).

Two important points, often overlooked in the literature, should be considered when assessing the operating characteristics of biomarkers:

- The characteristics of the population studied and of the “control group” (i.e., non-infected). For example, it is quite different to analyse a group of patients with a systemic inflammatory response (SIRS) following cardiac surgery (where the severity and prevalence of infection is low) to patients with SIRS within the context of pancreatitis evolving since >1 week, and both the severity and prevalence of infection are higher, with a high clinical impact of diagnosing infected pancreatitis necrosis (Dupuy et al, 2013).
- Criteria used as the “gold standard” for defining infection (or lack thereof) (Dupuy et al, 2013).

Two biomarkers fulfil the selection criteria and are routinely available: C-Reactive protein (CRP) and (PCT). Measuring CRP levels is a screen for infectious and inflammatory diseases.

CRP has been tested in various conditions, but only a few of these studies have focused on its use for optimising antibiotic therapy. A single, prospective, randomized, controlled trial performed in the 1990s in children is available; other studies have compared an intervention group to historical controls (Dupuy et al, 2013). Despite the few available studies confirming its usefulness, CRP measurements are widely used in children to adjust the duration of therapy. Several studies are ongoing, testing the usefulness of CRP measurements as an aid to shorten the duration of therapy in adult patients having sepsis, community-acquired pneumonia or exacerbation of chronic obstructive pulmonary disease (COPD) (Dupuy et al, 2013).

CRP can probably be used to help discontinuing therapy, although the evidence is limited. Procalcitonin has been more widely tested for optimising antibiotic therapy in
both children and adults. In adults presenting with community-acquired lower respiratory tract infections (LRTI), several randomized, controlled trials (RCTs) have tested the use of PCT as an aid to the initiation and/or discontinuation of antibiotics and have been summarised in a recent individual patient meta-analysis (Dupuy et al, 2013).

Four of these studies enrolled more than 900 patients hospitalised in intensive care or high dependency units. Two well-designed studies have been performed in children: one study included 121 neonates having early sepsis and another studied 384 children aged 1 to 36 months with acute fever of undetermined origin (Dupuy et al, 2013).

In view of these studies, the inclusion of PCT measurements within decision algorithms of antibiotic management for specific infections is likely appropriate. However, further studies are needed in infections which have been insufficiently examined so far (i.e., most infections other than LRTI) to better define the role of PCT in the antibiotic strategy (Dupuy et al, 2013).

Biomarkers are becoming increasingly important tools within all areas of medicine. Potential applications of biomarkers in infectious diseases include distinguishing bacterial from nonbacterial infection, monitoring response to therapy, and predicting outcomes. Continued research into a number of non-invasive urinary, serologic, and genetic biomarkers will help clinicians with diagnosis, prognosis, and treatment (Downes, 2012).

Following the literature as stated above the study wants to investigate the use of antimicrobials initially prescribed in the adult intensive care unit, and the cost associated with the use of antimicrobials.

2.5 Summary

The literature on the topics relevant to this study has been reviewed in this chapter. Topics included the introduction on antimicrobial stewardship, antimicrobial
stewardship and cost, antimicrobial use in the intensive care unit and a detailed discussion of infectious diseases biomarkers. The subsequent chapter provides an overview on the methodology used for the study.
CHAPTER 3

METHODOLOGY

3.1 Introduction

This chapter describes the methodology used to conduct the study in detail. The chapter starts with Section 3.1, an introduction and is followed by Section 3.2, the purpose of the study, Section 3.3, a description of the study site, Section 3.4, a description of the study design, Section 3.5, a description of the study period and Section 3.6, the study population and sample. Then follows Section 3.7, data collection and Section 3.8, data collection instruments, Section 3.9, statistical considerations, Section 3.10, reliability and validity of data, Section 3.11, pilot study, Section 3.12, bias and lastly Section 3.13, ethical considerations. The pilot study that was conducted prior to the data collection is followed by an explanation of the sample selection. The data collection instruments are individually discussed after which the data capturing and analysis procedures are outlined. Measures to ensure reliability and validity of data are provided followed by the ethical considerations for this study, which concludes the chapter. The word drug and medicine will be used interchangeably.

3.2 Purpose of the study

The purpose of the chapter was provided in Chapter 1 Section 1.4 and Section 1.5, page two and three.

3.3 Study site

The study was conducted in the medical adult intensive care unit (MICU) at Steve Biko Academic Hospital.

3.4 Study design

A descriptive quantitative study was conducted prospectively.
3.5 Study period

The study was done over a period of seven months where daily ward rounds were performed, either as pharmacy rounds, or within the multi-disciplinary team, and all new patients initiated on antimicrobials were included in the study.

3.6 Study population and sample

3.6.1 Study population

Patients admitted to the MICU at Steve Biko academic hospital during the study period.

3.6.2 Sample selection

All patients admitted to the adult medical intensive care unit at Steve Biko Academic Hospital during the study period that was initiated on antimicrobial therapy after admission was included in this study.

3.7 Data collection

For the purposes of the study, initially prescribed antibiotics were considered as the first course of antibiotics prescribed for each patient in the Intensive Care Unit. The antimicrobial that the patient was admitted with was documented, patients were mostly admitted from the casualty unit, and were already initiated on an antibiotic. Direct costs were calculated for the duration of therapy using the government tender prices and were related to treatment days. Patients admitted to the adult intensive care unit was recruited and initial antimicrobials were evaluated using the parameters as described in Table 3.1.
### Table 3.1: Antimicrobials Prescribing Markers

<table>
<thead>
<tr>
<th>Drug factors</th>
<th>Infectious biomarkers</th>
<th>Costs</th>
<th>Patient factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>WBC count</td>
<td>Defined daily cost, using Gauteng formulary.</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>Duration of use</td>
<td>CRP</td>
<td></td>
<td>Weight</td>
</tr>
<tr>
<td>Indication of use</td>
<td>Temperature</td>
<td></td>
<td>Renal marker</td>
</tr>
<tr>
<td></td>
<td>Blood culture</td>
<td></td>
<td>Hepatic markers</td>
</tr>
<tr>
<td></td>
<td>Procalcitonin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The patients admitted in the MICU were selected by the MICU medical team. Because of the high volumes of patients seen at SBAH the most critical patients with the best prognoses were admitted to the MICU. As new patients arrived in the MICU, the doctors evaluated the patient, did the necessary tests and prescribed the medication indicated for the patient. The patient was then seen by the researcher, where the patient’s file was used to get the patient’s history, including admitting vital signs, diagnoses etc. The patient’s medication was then evaluated for contraindications, interactions, duplications and dose. The physician was then contacted if any problems were identified. The patient was seen on a daily basis where vital signs, lab values and medication the patient received were documented. The patient was followed from admission in the MICU until the initially prescribed antibiotic was stopped. The above mentioned data was collected during this period.
3.8 Data collection Instruments

Data was collected as follows and recorded on the following appendices; refer to Figure 3.1 and Table 3.2. Patients were followed for the duration of their initially prescribed antibiotic course of therapy, for example: Patient X is admitted to the medical intensive care unit on amoxicillin, which is then replaced by meropenem in the unit. The amoxicillin is recorded as “Medication prior to review” (Appendix 1) and the first course of therapy was meropenem. This will then be recorded on the current drug therapy document (Appendix 2.4). This patient was followed for the duration of meropenem therapy, e.g. either stopped or de-escalated.

These instruments have been standardized by the American Society of Hospital Pharmacists in 1992 and have been validated in a South African context by Schellack in 2008 (Schellack & Gous, 2010).
Ward rounds done on a daily basis with physicians

Researcher evaluates patient charts for:

- **Patient factors**
  - (Appendix 1 Clinical Pharmacist notes)
  - (Appendix 2.2 Laboratory data)
  - (Appendix 2.3 Monitoring of vital signs)

- **Drug factors**
  - (Appendix 2.4 Current drug therapy)
  - (Appendix 3 Total cost of therapy)

- **Infectious biomarkers**
  - (Appendix 2.2 Microbiology)
  - (Appendix 2.2 Laboratory data)
  - (Appendix 2.3 Monitoring of vital signs)
  - (Appendix 2.4 Current drug therapy)

- **Costs**
  - (Appendix 3 Total cost of therapy)

**Figure 3.1: Data Collection**
Table 3.2: Data Collection Instruments and Objectives

<table>
<thead>
<tr>
<th>OBJECTIVE</th>
<th>INSTRUMENT OF MEASURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• To identify which antimicrobials were initially prescribed for an adult intensive care unit</td>
<td>Appendix 2.1 Microbiology</td>
</tr>
<tr>
<td></td>
<td>Appendix 2.4 Current drug therapy</td>
</tr>
<tr>
<td>• To determine if antimicrobials were prescribed according to patient diagnosis, weight, renal (urea and creatinine using Cockcroft and Gault) and hepatic markers (ALT, AST, GGT, Alk Phos, LDH, Total Bili and Direct Bili) as compared to the Standard Treatment Guidelines</td>
<td>Appendix 2.1 Microbiology</td>
</tr>
<tr>
<td></td>
<td>Appendix 2.2 Laboratory data</td>
</tr>
<tr>
<td></td>
<td>Appendix 2.3 Monitoring of vital signs</td>
</tr>
<tr>
<td></td>
<td>Appendix 2.4 Current drug therapy</td>
</tr>
<tr>
<td>• To investigate the use of antimicrobials against infection biomarkers (WBS count, CRP, temperature, blood culture, procalcitonin.) considering indication, dose and duration of treatment as compared to the Standard Treatment Guidelines</td>
<td>Appendix 2.1 Microbiology</td>
</tr>
<tr>
<td></td>
<td>Appendix 2.2 Laboratory data</td>
</tr>
<tr>
<td></td>
<td>Appendix 2.3 Monitoring of vital signs</td>
</tr>
<tr>
<td></td>
<td>Appendix 2.4 Current drug therapy</td>
</tr>
<tr>
<td>• To determine the direct costs associated with the initially prescribed antimicrobial therapy for a patient in a medical adult intensive care unit using daily defined dose</td>
<td>Appendix 3 Total Cost of Therapy</td>
</tr>
</tbody>
</table>
Appendix 1: Clinical pharmacist notes on admission – This appendix contains the patients demographic and administrative information, no personal information is used which can identify the patients. This information is only used to get the patient’s gender and age and to obtain the patient’s laboratory data from the National Health Laboratory System (NHLS). This appendix also contains the patient’s diagnosis according to affected organ system and the disease state of the patient. The patient’s vital signs on admission and the medication prior to admission (grouped according to the ATC codes) are noted in this appendix.

Appendix 2.1: Microbiology – All microbiological tests performed on the individual patient, e.g., blood or urine cultures and the organism that was cultured.

Appendix 2.2: Laboratory data – All the laboratory data that was documented on a regular basis to monitor the patients fluid states, renal and hepatic function, infectious markers etc.

Appendix 2.3: Monitoring of vital signs – The patient’s daily weight and vital signs (temperature, blood pressure, pulse and respiration) was documented. The highest and lowest of the patient’s vital signs for the 24-hour period was also documented.

Appendix 2.4: Current drug therapy – The medication that was used while the patient was in the MICU was noted on this appendix. The drug, dose and route of administration was noted as well as the start and stop date of each medication.

Appendix 3: Total cost of therapy – The cost of each unit antibiotic or pack size was multiplied by times administered daily to get the daily cost then it was multiplied by the days on antibiotic to get the total cost per treatment.

3.9 Statistical considerations

3.9.1 Sample size

Sample size estimation was done by a biostatistician and was estimated on 50 patients for the purposes of the study. During the study period of seven months 52 patients were admitted.
3.9.2 Statistical analysis

The data was captured into a Microsoft Excel™ spread sheet. Laboratory data was obtained from the laboratory servicing the patients at Steve Biko Academic Hospital. Personal patient information was part of the ASP implementation. The direct costs of the patient’s initial antimicrobial usage were calculated as stated above.

The statistical analysis was considered explorative and was of a descriptive nature. Continuous variables were summarized by sample; mean, standard deviation, median, quartile range, minimum and maximum values. Categorical variables was summarised by frequency counts and percentage calculations.

The primary objective of the study was to determine the appropriateness of the correct initial antimicrobials for an individual patient, and it was assessed by using the antimicrobial prescribing markers. The check list with 13 criteria (Table 3.1) was used to determine the appropriateness of the initial antimicrobial for an individual patient. The number of correctly followed procedures was expressed as a percentage out of 13. For each percentage calculation 95 % confidence interval was calculated.

The initial prescribed antimicrobials were categorised and summarised descriptively.

The cost of initial antimicrobials was expressed as cost per defined daily dose (DDD).

All statistical procedures were performed on SAS, Release 9.3.

3.10 Reliability and validity of data

Reliability was achieved by standardizing the measurement procedure by using a formulary restriction for some antimicrobials. Data validation was done following the principals laid by the Guidelines for Good Clinical Practice of Clinical Trials with Human Participants in South-Africa (Department of Health, Second addition, 2006).

According to Leedy & Ormrod (2001) reliability was the extent to which a measuring instrument or -tool was able to provide the same results when the entity being measured has not changed. Reliability during a research study can be improved with
the use of a pilot study. A pilot allowed the researcher the opportunity to become familiar with the procedures, materials and apparatus that was used during the research study.

3.11 Pilot Study

Reliability and validity of the collection instruments was tested during the pilot study: changes were then made accordingly. A pilot study was conducted in the surgical intensive care unit using five patients, where they were seen on a daily basis and, newly initiated antibiotics were recorded. The patients were followed until the initiated antibiotics were stopped. The pilot study measured the stability, internal consistency and equivalence of the instruments. Face validity was used to relate the appropriateness and acceptability of the tool in the target population. No amendments were made to the data collection instruments following the pilot study.

3.12 Bias

The researcher visited the medical adult intensive care unit daily for the duration of the study. The required information was obtained from the patient’s clinical parameters, and antimicrobials usage was monitored. The researcher functioned within the multi-disciplinary team and all data was cross-checked by the clinical supervisor, this was to ensure that no bias was introduced.

3.13 Ethical considerations

Ethical approval was obtained from the University of Pretoria (number 178/2012) and the University of Limpopo - MEDUNSA CAMPUS (number MREC/H/212/2012: PG)

A letter for intent to conduct the study was drafted and handed to the CEO of Steve Biko Academic Hospital. (Refer Appendix 4).

Participant consent was not obtained for this study. This was an epidemiological observation and participant personal data was not collected. Participant personal information was only used to match the laboratory report obtained from the laboratory dataset with the dataset that is hosted at SBAH.
The researcher arranged for the retention of study documentation until the end of the study. In addition the researcher was complied with specific local regulations/recommendations with regards to patient record retention.
CHAPTER 4

JOURNAL ARTICLE

Investigating initial antimicrobial use in a medical adult intensive care unit: at Steve Biko Academic Hospital, Pretoria, South Africa

4.1 Introduction

The results and discussion will be presented as a journal article. This will be submitted to the South African Journal of Infectious Diseases. An outline of author guidelines is provided as Appendix 5.

4.2 Background

Antimicrobial resistance is increasing globally. It is estimated that in hospitals around the world 50% of antimicrobial usage is either unnecessary or inappropriate.\textsuperscript{1,2} The timely selection and administration of appropriate antimicrobial therapy can significantly impact treatment outcomes, especially in patients with severe or life-threatening infections.\textsuperscript{3}

Antimicrobial stewardship is a coordinated effort to ensure the judicious and effective use of antimicrobial therapy that includes but is not limited to the appropriate selection, dosing, route of administration, and duration of antimicrobial therapy.\textsuperscript{2} The goal of an antimicrobial stewardship programme (ASP) is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use and reducing health care costs without adversely affecting quality of care.\textsuperscript{2}

Surviving sepsis campaign recommends prompt antimicrobial therapy in high risk patients. Inappropriate antimicrobial therapy for septic shock is associated with a fivefold reduction in survival.\textsuperscript{4} Appropriate antibiotic use is of both clinical and economic significance to any health system and should be given adequate attention.\textsuperscript{5} Pharmacists play an important role in reducing the threat to public health and costs of hospital-acquired antibiotic-resistant infections through antimicrobial stewardship.\textsuperscript{2}
The implementation of an ASP can present a challenge because of limited resources and other barriers. Institutional needs and available resources should be taken into consideration in planning a strategy for ASP implementation. It should optimize the use of limited resources, overcome barriers to implementation, and improve clinical outcomes.\(^2\) Biomarkers are used as part of an antimicrobial stewardship program, when treating bacterial infection and sepsis. Procalcitonin (PCT) is used to shorten antimicrobial therapy without adversely affecting clinical outcomes.\(^2\)

This study aimed to explore factors surrounding initially prescribed antibiotics and direct medicine related costs in the Medical Intensive Care Unit (MICU), at Steve Biko Academic Hospital. For the purpose of this study initially prescribed antibiotics were defined as all antibiotic prescriptions initiated in the MICU. At the time of the study, an antibiotic policy was not available for the MICU.

### 4.3 Methods

#### 4.3.1 Study site

The study was conducted in the MICU at Steve Biko Academic Hospital (SBAH). The hospital contains 832 beds of which 53 are ICU beds, 21 high care beds and a theatre complex of 21 operating theatres (19 is active).\(^6\) The MICU with nine beds is the only ICU in the hospital that admits medical patients. The ward never has more than six beds occupied because of a shortage of ICU-trained nursing staff.

#### 4.3.2 Study population and sample

All patients admitted to the adult MICU who received a prescription for antimicrobial therapy were included in the study. According to the statistics in the ward the average amount of patients admitted to the MICU is 24 patients per month depending on the staff complement and availability.\(^7\)
4.3.3 Data collection and data collection instruments

For the purposes of the study, antibiotics prescribed after admission to the MICU were considered as the first course of antibiotics. The antimicrobial that the patient was admitted with was documented and are referred to as “medication prior to review”. Only antibiotics that were initiated were included in the study. Direct costs were calculated for the duration of therapy using the government tender prices and were related to treatment days. Patients admitted to the MICU was recruited and initial antimicrobial use was evaluated using the parameters as described in Table 1 and in consultation with the treating physician or infectious disease specialist.

Table 4.1: Antimicrobials Prescribing Markers

<table>
<thead>
<tr>
<th>Drug Factors</th>
<th>Infectious Biomarkers</th>
<th>Costs</th>
<th>Patient factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dose</td>
<td>• WBC count</td>
<td>Defined daily cost, using Gauteng formulary and National Department of Health Tender prices.</td>
<td>• Diagnosis</td>
</tr>
<tr>
<td>• Duration of use</td>
<td>• CRP</td>
<td></td>
<td>• Weight</td>
</tr>
<tr>
<td>• Indication of use</td>
<td>• Temperature</td>
<td></td>
<td>• Renal marker</td>
</tr>
<tr>
<td></td>
<td>• Blood culture</td>
<td></td>
<td>• Hepatic markers</td>
</tr>
<tr>
<td></td>
<td>• Procalcitonin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data was collected using a validated data collection instrument developed by the American Society of Hospital Pharmacists (1992) that has been validated in a South African setting.
Patients were followed for the duration of their initially prescribed antibiotic course for example: Patient X is admitted to the medical intensive care unit on amoxicillin, and switched in the unit to meropenem. The amoxicillin was recorded as “medication prior to review” and meropenem as the “initially prescribed antibiotics”. Patient X was then followed for the duration of meropenem therapy, e.g. either stopped or de-escalated.

The cost was derived by using the following equation: Daily cost = (antibiotic pack size x dosing interval) x days on antibiotics. The cost of antibiotics was derived using the National Department of Health’s tender prices for 2012.

4.3.4 Statistical analysis

The data was captured on a Microsoft Excel™ spread sheet. Laboratory data was obtained from the National Health Laboratory System (NHLS), which provides services to the patients at Steve Biko Academic Hospital. The direct cost of the patient’s initial antimicrobial usage was calculated by using the National Department of Health’s Tender prices according the daily defined dose.

The statistical analysis was considered explorative and was of a descriptive nature. Continuous variables were summarized by sample size; mean, standard deviation, median, quartile range, minimum and maximum values. Categorical variables were summarised by frequency counts and percentage calculations.

All statistical procedures were performed on SAS® (SAS institute Inc. Cary, NC), Release 9.3.

The initially prescribed antimicrobials were categorised and summarised descriptively. The cost of initial antimicrobials in a MICU at Steve Biko Academic Hospital was classified as the defined daily dose (DDD).
4.3.5 Ethical considerations

Ethical approval was obtained from the University of Pretoria (Number 178/2012) and the University of Limpopo - Medunsa Campus (Number MREC/H/212/2012: PG).

Participant consent was not obtained for this study. This study was considered as an observational study. Participant personal information was only used to match the laboratory report obtained from the laboratory dataset with the dataset that is hosted at SBAH. Once this was done, the patient's personal data was anonymised.

4.4 Results

4.4.1 Patient demographics

All patients admitted to the adult MICU at SBAH that were initiated on antimicrobial therapy were included in this study. Over the study period of seven months, 52 patients were admitted to the study.

4.4.1a Patient Gender

Of the 52 patients included during the study 23 patients were male (44%) and 29 patients were female (56%).

4.4.1b Patient age and weight

The mean age of the patients admitted to the study was 40 years, with a range of 13 to 77 years. The mean weight of patients admitted to the study was 74.29 kg, with a range of 27kg to 120kg. The age and weight distribution is illustrated in Table 2.
Table 4.2: Age and weight Distribution

<table>
<thead>
<tr>
<th>Variable Label</th>
<th>N</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52</td>
<td>40.08</td>
<td>17.96</td>
<td>34</td>
<td>13</td>
<td>77</td>
</tr>
<tr>
<td>Weight</td>
<td>52</td>
<td>74.29</td>
<td>16.90</td>
<td>74</td>
<td>37</td>
<td>120</td>
</tr>
</tbody>
</table>

4.4.2 Initiation of Antibiotics

The majority of patients, 23 (44%; n = 52) were initiated on antibiotics on day one of admission to the MICU. Twelve (23%; n = 52) patients were initiated on day two and five (10%; n = 52) patients were initiated on day three. The remainder of the patients were initiated on days: four (2%; n= 52), five (6%; n= 52), six (4%; n= 52, seven (8% n= 52) and eight (2%; n= 52).

Of the 76 antibiotics prescribed initially, the majority 54 (71%) was started on the same day the prior antibiotics were discontinued. Eight (11.11%) antibiotics were started one day after the prior antibiotics were stopped. The remainder of the ten patient’s antibiotics were started 3 - 12 days after the prior antibiotics were stopped.

4.4.3 Length of Hospital Stay

The mean length of hospital stay (LOS) in the MICU for all patients was 10.63 days (range 3 to 23 days) with a standard deviation of 4.90 days and a median of 10.50 days.

4.4.4 Antibiotics most frequently prescribed and the related cost

During the study period 76 antibiotics was started for the 52 patients. The three antibiotics most frequently prescribed during the study period were meropenem, 19 times, piperacillin/tazobactam ten times and clarithromycin, nine times.

The mean cost of treatment for these three most frequently prescribed antibiotics were meropenem with an average cost of treatment of R6 335.31c,
piperacillin/tazobactam with an average cost of treatment of R1 867.02 and clarithromycin with an average cost of treatment of R2 136.95, for their respective treatment periods.

The total cost for initial antibiotic use during the study period was R209 140.40, with an average cost for all initial antibiotics of R28 400.93.

Table 3 illustrates costs associated with antibiotics use in the MICU.
Table 4.3: Cost of Antibiotic Use in the MICU

<table>
<thead>
<tr>
<th>Organ system</th>
<th>ATC code</th>
<th>International propriety name</th>
<th>Number of patients</th>
<th>Mean days on antibiotic</th>
<th>Mean cost per day on antibiotic (R)</th>
<th>Mean cost per treatment (R)</th>
<th>Mean DDD (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-infectives for systemic use</td>
<td>J01DH02</td>
<td>Meropenem</td>
<td>19</td>
<td>7.5</td>
<td>890.68</td>
<td>6335.31</td>
<td>3.26</td>
</tr>
<tr>
<td></td>
<td>J01CR05</td>
<td>Piperacillin/tazobactam</td>
<td>10</td>
<td>5.3</td>
<td>354.09</td>
<td>1867.02</td>
<td>14.85</td>
</tr>
<tr>
<td></td>
<td>J01FA09</td>
<td>Clarithromycin</td>
<td>9</td>
<td>8.4</td>
<td>253.06</td>
<td>2136.95</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>J01XX08</td>
<td>Linezolid</td>
<td>5</td>
<td>5.2</td>
<td>601.76</td>
<td>3129.15</td>
<td>1.20</td>
</tr>
<tr>
<td></td>
<td>J01DD04</td>
<td>Ceftriaxone</td>
<td>5</td>
<td>5.4</td>
<td>45.12</td>
<td>243.65</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>J01CF02</td>
<td>Cloxacillin</td>
<td>4</td>
<td>6.0</td>
<td>193.16</td>
<td>1229.20</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>J01DH51</td>
<td>Imipenem</td>
<td>3</td>
<td>6.7</td>
<td>762.96</td>
<td>5001.63</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>J01XA02</td>
<td>Teicoplanin</td>
<td>3</td>
<td>6.7</td>
<td>299.26</td>
<td>1995.07</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>J01XA01</td>
<td>Vancomycin</td>
<td>3</td>
<td>6.7</td>
<td>89.04</td>
<td>593.60</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>J01CR02</td>
<td>Co-amoxiclav</td>
<td>6</td>
<td>6.0</td>
<td>47.25</td>
<td>283.50</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>J01EE01</td>
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|              | Mean (N= 16) |                       |                    |                         |                                   |                           |              |
|              | Mean (N= 16) | 6.023188               | 278.16             | 1775.06                 | 3.23                              |                           |              |
|              | SD           | 1.220944               | 298.01             | 1949.56                 | 3.99                              |                           |              |
|              | Min          | 3                      | 5.88               | 17.63                   | 0.1                               |                           |              |
|              | Max          | 8.44                   | 890.68             | 6335.31                 | 14.85                             |                           |              |
|              | Median       | 6                      | 174.48             | 1159.87                 | 2                                 |                           |              |
4.4.5 Diagnoses

Figure 1, illustrates the number of times the different organ systems \((n = 149)\) were affected. The Figure illustrates that; “infectious diseases” was diagnosed the most, followed by diagnoses made related to the endocrine-metabolic system.

**Figure 4.1: Systems affected.**

During the study period 167 diagnoses were made for the 52 patients (mean diagnoses of 3.2 per patient).

Diagnoses most commonly made during this study was sepsis - 11 times (6.58%, \(n=167\)), community acquired pneumonia (CAP), hypertension and respiratory failure - 8 times (4.8%, \(n=167\)).

4.4.6 Number of antibiotics used during the hospital stay

During the study, 76 antibiotics were prescribed for the 52 patients (mean 1.38 antibiotics per patient). The antibiotics were prescribed as follows:
- β-lactams, 48 (63.15%; n= 76) :
  (Carbapenems, 22 (28.94%; n= 76)
  (Penicillins, 20 (26.31%; n= 76)
  (Cephalosporins, 6 (7.9%; n= 76)
- Macrolides, 9 (11.84%; n= 76)
- Glycopeptides, 6 (7.89%; n= 76)
- Oxazolidinones, 5 (6.58%; n= 76)
- Aminoglycosides, 2 (2.63%; n= 76)
- Trimethoprim/sulfamethoxazole, 2 (2.63%; n= 76)
- Metronidazole, 2 (2.63%; n= 76)
- Clindamycin, 1 (1.31%; n= 76)
- Tigecycline, 1 (1.31%; n= 76)

During the study 38 (73.07%; n=52) patients were started on one antibiotic, ten (19.23%; n=52) patients were started on two antibiotics, three (5.77%; n=52) patients were started on three antibiotics and one (1.92%; n=52) patient was started on four antibiotics (ceftriaxone, cloxacin, co-trimoxazole and claritromycin)

### 4.4.7 Infection Biomarkers

Figure 2 illustrates the patient infection biomarkers (C-reactive protein (CRP), PCT white blood cell count (WBC) and temperature) one day prior to initiation of initially prescribed antibiotics (the day before antibiotics was prescribed) as well as the day of initiation.

**Temperature**

Seventeen patients (33%; n = 52) were admitted to the MICU with a raised temperature with a mean value of 37.18°C (considered as above 37.0 °C). The majority of the study population 31 (60%; n=52) who were initiated on antibiotics in the MICU, had a raised temperature with a mean value of 37.59°C.

**C-reactive protein (CRP)**
The majority of the patients 32 (61.5%; n = 52) of patients were admitted in the MICU with a raised CRP with a mean value of 198.21mg/l (considered as above 5mg/l). Almost all patients 51(98 %; n = 52) initiated on antibiotics in the MICU had a raised CRP with a mean value of 208.92mg/l.

**Procalcitonin (PCT)**

About half of the patients 25 (48%; n= 52) were admitted with an elevated PCT with a mean value of 42.33ng/ml (considered as above 0.00-0.05ng/ml). In the majority of the study population 46 (88%; n= 52) PCT was elevated on the day antibiotics were initiated with a mean value of 31.75ng/ml.

**White blood cell (WBC)**

Less than half of the patients 20 (38.5%; n = 52) were admitted with a raised WBC count with a mean value of 11.90 10^9/l (considered as above 3.92-9.88 10^9/l). The majority of the study population’s 31 (60%; n=52 patients) WBC count was more elevated on the day antibiotics were initiated with a mean value of 14.48 10^9/l.

![Figure 4.2: Prior/initial infection biomarkers](image)

**Figure 4.2: Prior/initial infection biomarkers**

**Normal values:**

- PCT: 0.00-0.05ng/ml
- CRP: below 5mg/l
- WBC: 3.92-9.88 10^9/l
- Temperature: 37.0°C
4.4.8 Cultures obtained

The number of positive cultures for all micro-organisms, according to specimen origin before or on the day when the initial antibiotic was prescribed, are illustrated in Figure 3.

The results of cultures obtained are illustrated in Figure 3. During the study period a 109 positive cultures were obtained, with 55 positive cultures obtained from blood samples, 25 tracheal aspirate, 12 urine, 11 sputum, 3 bronchial lavage, 2 catheter tip and 1 stool culture was obtained.

![Figure 4.3: Positive cultures and specimen origin](image)

Table 4 describes all micro-organisms cultured before and on the day the initially prescribed antibiotic was started. In most of the patients cultures was taken before antibiotics was started.

Of the 109 positive cultures taken before the initially prescribed antibiotic was started, 64 were positive for bacteria. The rest of the 45 positive organisms were of viral, fungal, mycobacterium and parasitical origin. Of the 64 positive cultures taken, 35 (55%; n= 64) were Gram negative Bacilli and 19 (36.5%; n= 64) were Gram-
positive cocci. Both *Acinetobacter baumannii*, and coagulase negative staphylococci (CoNS) were cultured nine times.
Table 4.4: Cultures prior to the initiation of initial antibiotics.

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<td>Pseudomonas aeruginosa</td>
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<td>Serratia</td>
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<td><strong>GRAM POSITIVE COCCI</strong></td>
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<tr>
<td>Coagulase-negative staphylococci (CONS)</td>
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<tr>
<td>Enterococcus faecalis</td>
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<td>Methicillin-resistant Staphylococcus aureus (MRSA)</td>
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<td>Staphylococcus aureus</td>
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<tr>
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<td>1</td>
</tr>
<tr>
<td>Vancomycin resistant enterococci (VRE)</td>
<td>1</td>
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<tr>
<td><strong>GRAM NEGATIVE COCCI</strong></td>
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</table>

*No specific strain was listed, reflected as stated on the laboratory report*
4.4.9 Appropriate use of antibiotics

Antibiotic use would be considered appropriate when complying with the parameters as described in Table 1.

In consultation with the infectious diseases specialist in some patients, the results indicated that that the majority, 46 (60%; n=76) of all initially prescribed antibiotics in the MICU were prescribed appropriately, with 30 (40%; n=76) antibiotics being prescribed inappropriately. Reasons for inappropriate antibiotic use were as follows (measured using parameters specified in Table 4.1):

- Three antibiotics were initiated on patients with normal inflammation biomarkers.
- Six antibiotics were initiated on patients with no positive cultures and no raised inflammation markers.
- Ten antibiotics were initiated on patients with no positive cultures.
- Eleven antibiotics were inappropriately prescribed according to the sensitivity patterns.

4.5 Discussion

More females (56 %) were admitted to the study and this reflects the South African population according to Statistics South Africa (2011).\(^\text{15}\)

The mean age (40.08 years) of the patients admitted to the MICU was in line with a similar study.\(^\text{16}\) This age group constitutes patients that are economically active in the society.

The mean duration of stay was 10.63 days (range 3 to 23 days) in this study. This is in line with international\(^\text{17}\) and local literature as a similar study conducted at Groote Schuur Hospital in Cape Town, South Africa, also reported similar results.\(^\text{18}\)

During the study the infection biomarkers that were obtained (WBC, CRP, PCT and temperature), were all raised prior to initiation of antibiotics. These biomarkers were used to guide antibiotic use. Over the past two decade’s PCT, CRP, WBC have been extensively studied as a serum marker of systemic infection and sepsis.\(^\text{19}\) PCT guided therapy is not only beneficial for respiratory tract infections but also provide
useful guidance for antimicrobial treatment in critically ill patients in the ICU who are treated for suspected bacterial infections.¹⁹

Half of the patient population, 26 (50 %; n = 52) had sepsis or an infective diagnosis made with the assistance of blood cultures. Specifically, positive “sterile site” cultures (such as blood cultures) better represent true infection than positive “non-sterile site” cultures (such as wound and sputum cultures). Non-sterile sites are more likely to reflect colonization or contamination.²⁰ According to the Surviving Sepsis Campaign (2014), at least two sets of blood cultures (both aerobic and anaerobic bottles) should be obtained before antimicrobial therapy is initiated.⁴

The antibiotics that were mostly prescribed during the study period were meropenem, 19 (25%; n = 76) followed by piparicillin/tazobactam 10 (13.15% n = 76) both of these drugs are part of the β – lactam group. According to a study done in 2012, β – lactams including carbapenems, are the most frequently prescribed antibiotics in empiric therapy in patients with severe sepsis and septic shock.²¹

Meropenem was the drug most frequently prescribed 19 (25%; n = 76) as initial antibiotic therapy for patients admitted to the MICU. This is in line with the Surviving Sepsis Campaign (2014) that states a broad spectrum antibiotic is indicated as first line therapy in patients with sepsis.⁴

This drug was also the most expensive first line therapy at a mean daily cost of R890.68. According to a study done in a large tertiary care academic medical centre meropenem was also the most expensive antibiotic.²²

The choice of meropenem as first line therapy was approved by the infectious diseases specialist for patients with contributing co-morbidities that could lead to their demise.

Piperacillin/tazobactam was prescribed in ten patients (n = 52) with an average daily cost of R354.09. In a study conducted in a National Multicentre in Spain β-lactams are the mainstay of empiric therapy in patients with severe sepsis and septic
shock.\textsuperscript{21} This is concurred by another study where it stated that piperacillin/tazobactam is a good empiric therapy for a patient in an ICU setting with community acquired pneumonia (CAP).\textsuperscript{23}

Empiric therapy should attempt to provide antimicrobial activity against the most likely pathogens based upon each patient’s presenting illness and local patterns of infection.\textsuperscript{4}

Clarithromycin was mostly used as dual therapy in CAP. Clarithromycin is effective against commonly encountered pathogens and are well tolerated.\textsuperscript{24} A patient with CAP in an ICU setting will benefit from the addition of azithromycin.\textsuperscript{23} Azithromycin was not freely available in SBAH to use for CAP, and clarithromycin was used instead of azithromycin.

The majority of antibiotics 46 (60\%) were prescribed appropriately and 30 (40\%) antibiotics were prescribed inappropriately, according to weight, renal function (creatinine clearance), hepatic function, infection biomarkers (WBS count CRP, temperature, blood culture procalcitonin). This was discussed in section 4.4.9. When using indication, dose and duration of treatment it was compared to the Standard Treatment Guidelines and Essential Drug List for Adults at Hospital Level (year) and other relevant literature. This is contradictory to studies done to investigate antimicrobial use in ICU’s.

During a study done in 2011, 221 patients were identified with hospital acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) and it was found that just less than half of 107 (48\%) patients received adequate initial intravenous antibiotic therapy vs. 114 (53\%) that received inadequate initial intravenous antibiotic therapy.\textsuperscript{16}

During a study done in 2012 on antibiotic prescription practices and their relationship to outcome in South African intensive care units, therapeutic antibiotics were initiated in 182 patients, just more than half (54.9\%) received inappropriate initial antibiotic therapy.\textsuperscript{25}
4.6 Conclusions

During the study it was found that the β-lactams were the mainstay of initially prescribed antimicrobial therapy in the MICU. This is in line with what was found in literature.

The majority of initially prescribed antibiotics were prescribed appropriately while the remainder of antibiotics were prescribed inappropriately. This is contrary to what was found in literature.

The total cost for initial antibiotics during the study period was R209 140.40, with an average cost for all initial antibiotics of R28 400.93. No similar studies were performed in an Academic Hospital in South Africa where rand values could be compared. But a similar study done in 2012 in the USA in a tertiary care academic medical center found the cost of antibiotics is higher as compared to this study.

Initial antibiotic use of antibiotics was mostly appropriate in the MICU; however the addition of an antibiotic policy and training might ensure continuous rational antibiotic use.
REFERENCES

9. Untiedt SM. The impact of pharmaceutical care provided by Medunsa / Technikon Pretoria BPharm IV students at Ga-Rankuwa


13. Bronkhorst E. An assessment of the need of pharmaceutical services in the Intensive Care Unit and High Care Unit of Steve Biko Academic Hospital. MSc (Med) Pharmacy Dissertation. Department of Pharmacy, University of Limpopo, Medunsa Campus. 2012.


17. Wilke MH, Grube RF, Bodmann KF. Guideline-adherent initial intravenous antibiotic therapy for hospital-acquired/ventilator-associated pneumonia is clinical superior, saves lives and is


CHAPTER 5

SUMMARY OF RESULTS, CONCLUSION, RECOMMENDATIONS AND LIMITATIONS

5.1 Introduction

In this chapter, a summary of the results and conclusions will be presented. Based on the results of the study, recommendations for practice will be offered. The chapter will end with limitations encountered during the study.

5.2 Summary of Results

Of the 52 patients included during the study 23 patients were male (44%) and 29 patients were female (56%).

The mean length of hospital stay (LOS) in the MICU for all patients was 10.63 days (range 3 to 23 days).

The average cost of the top three initially prescribed antibiotics that were prescribed during the study period was as follows: Meropenem, with an average cost of treatment of R6 335.31c. Pip/Taz with an average cost of treatment of R1 867.02c and claritromycin with an average cost of treatment of R2 136.951c. The total cost for initial antibiotics during the study period was R209 140.40c.

During the study, 76 antibiotics were prescribed for the 52 patients. 48 of the prescribed antibiotics were β – Lactams, (22 carbapenem’s 20 penicillin’s and six cephalosporins) nine were macrolides, six were glycopeptides, five were oxazolidinones, two were aminoglycosides, trimethoprim/sulfamethoxazole and metronidazole were prescribed twice, and Clindamycin and Tyge cycline were prescribed once.

During the study 38 patients were initiated on one antibiotic, 10 patients were initiated on two antibiotics, three patients were initiated on three antibiotics and one patient was initiated on four antibiotics.
The top three initially prescribed antibiotics prescribed during the study period were meropenem (19 times), Pip/Taz (10 times) and Claritromycin, (9 times). 46 (60%) Antibiotics were prescribed appropriately and 30 (40%) Antibiotics were prescribed inappropriately.

Temperature

Seventeen patients (33%; n = 52) were admitted to the MICU with a raised temperature with a mean value of 37.18°C (considered as above 37.0 °C). The majority of the study population 31 (60%; n=52) who were initiated on antibiotics in the MICU, had a raised temperature with a mean value of 37.59°C.

C-reactive protein (CRP)

The majority of the patients 32 (61.5%; n = 52) of patients were admitted in the MICU with a raised CRP with a mean value of 198.21mg/l (considered as above 5mg/l). Almost all patients 51(98 %; n = 52) initiated on antibiotics in the MICU had a raised CRP with a mean value of 208.92mg/l

Procalcitonin (PCT)

About half of the patients 25 (48%; n= 52) were admitted with an elevated PCT with a mean value of 42.33ng/ml (considered as above 0.00-0.05ng/ml). In the majority of the study population 46 (88%; n= 52) PCT was more elevated on the day antibiotics were initiated with a mean value of 31.75ng/ml.

White blood cell (WBC)

Less than half of the patients 20 (38.5%; n = 52) were admitted with a raised WBC count with a mean value of 11.90 $10^9$/l (considered as above 3.92-9.88 $10^9$/l). The majority of the study population’s 31 (60%; n=52 patients) WBC count was more elevated on the day antibiotics were initiated with a mean value of 14.48 $10^9$/l.

109 positive cultures were obtained during the study period with 55 positive blood cultures, 25 positive tracheal aspirate cultures, 12 positive urine cultures, 11 positive sputum cultures, 3 positive bronchial lavage cultures, 2 positive catheter tip cultures and 1 positive stool culture.
5.3 Conclusion

During the study it was found that meropenem was the mainstay of initially prescribed therapy in a MICU at SBAH. The total cost for initial antibiotics during the study period was R209 140.40, with a mean cost for all initial antibiotics of R28 400.93.

60% of initially prescribed antibiotics were prescribed appropriately according to weight, renal function (Creatinin Clearance), hepatic function, infection biomarkers, (WBS count CRP, temperature, blood culture procalcitonin) indication, dose and duration of treatment. It was then compared to the standard Treatment Guidelines and Essential Drug List for Adults at Hospital Level.

By making antimicrobial stewardship part of our daily practice, we can improve patient safety and care, reduce the unnecessary use of valuable resources, and reduce resistance (Doron S and Davidson LE, 2011).

5.4 Limitations and Recommendations

The following limitations and recommendations were made based on the results of the study:

- The sample size was limited, conduct a larger study in more ICU’s with more patients allowing a better representation of the study results
- Guidelines specifying appropriate/inappropriate antibiotic use were not in place; an antibiotic policy should be written and implemented in the MICU as well as in the whole of the hospital.
REFERENCES


Bronkhorst E. 2012. An assessment of the need of pharmaceutical services in the Intensive Care Unit and High Care Unit of Steve Biko Academic Hospital. MSc (Med) Pharmacy Dissertation. Department of Pharmacy, University of Limpopo, Medunsa Campus.


Untiedt SM. 2004. The impact of pharmaceutical care provided by Medunsa / Technikon Pretoria BPharm IV students at Ga-Rankuwa Hospital. MSc (Med)

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<td>Other</td>
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## APPENDIX 2: PHARMACEUTICAL MONITORING FORM

### MICROBIOLOGY

<table>
<thead>
<tr>
<th>Date</th>
<th>Blood culture</th>
<th>Organisms isolated</th>
<th>Sensitivity</th>
<th>Antimicrobial prescribed</th>
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**DATE AND REASON FOR ANTIMICROBIAL THERAPY TO BE DISCONTINUED OR CHANGED**

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<th>Date</th>
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## APPENDIX 2.2: LABORATORY DATA

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<tr>
<th></th>
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<tr>
<td><strong>UREA (mmol/L)</strong></td>
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<td><strong>CREAT (umol/L)</strong></td>
<td></td>
<td>53 - 106</td>
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<tr>
<td><strong>TOTAL PROTEIN (g/L)</strong></td>
<td></td>
<td>58 - 76</td>
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<tr>
<td><strong>ALBUMIN (g/L)</strong></td>
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<td>32 - 46</td>
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<tr>
<td><strong>WBC (10^9/L)</strong></td>
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<tr>
<td><strong>Neutrophils (%)</strong></td>
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<tr>
<td><strong>Neut abs (10^9/L)</strong></td>
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<td><strong>Lymphocytes (%)</strong></td>
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<td>20 - 40</td>
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<td><strong>Lymph abs (10^9/L)</strong></td>
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<tr>
<td><strong>Monocytes (%)</strong></td>
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<td>2 - 10</td>
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<tr>
<td><strong>Mono abs (10^9/L)</strong></td>
<td></td>
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<td><strong>Eosinophils (%)</strong></td>
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<td><strong>Basophils (%)</strong></td>
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<td>150 - 450</td>
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<td><strong>AST (IU/L)</strong></td>
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<td><strong>ALK.PHOS (IU/L)</strong></td>
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<td><strong>TOT BILI (umol/L)</strong></td>
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<td>5 - 21</td>
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<td><strong>DIRECT BILI (umol/L)</strong></td>
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<td><strong>GGT (IU/L)</strong></td>
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<td><strong>CRP (mg/L)</strong></td>
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<tr>
<td><strong>Procalcitonin (ng/ml)</strong></td>
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## APPENDIX 2.3

### MONITORING OF VITAL SIGNS

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## CURRENT DRUG THERAPY

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### APPENDIX 3: Total cost of therapy

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<tr>
<th>Date</th>
<th>Patient Number</th>
<th>Item as prescribed per day</th>
<th>Total Daily Dose</th>
<th>Formulation</th>
<th>Pack size</th>
<th>Price per pack size</th>
<th>Prescribed Daily Dose</th>
<th>Daily Cost</th>
<th>Total amount of days on therapy and cost for duration</th>
<th>Therapy indicated yes or no (according to bio-markers and STG)</th>
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<tr>
<td>2012/02/13</td>
<td>Example</td>
<td>Augmentin 1000 mg bd</td>
<td>1000 mg</td>
<td>Tablets 250 mg</td>
<td>Container 15's</td>
<td>R17.23</td>
<td>1000mg (8 tablets per day)</td>
<td>R 9.18</td>
<td>10 days at a total cost of R91.80</td>
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APPENDIX 4: LETTER OF INTENT TO THE HOSPITAL SUPERINTENDENT STEVE BIKO ACADEMIC HOSPITAL

Dr BJ Ribeiro
Steve Biko Academic Hospital

Dear Dr Ribeiro

Letter of intent to conduct an operational study

We are hereby requesting for Regina Jacobs to conduct a study in the Adult Intensive Care Unit at Steve Biko Academic Hospital. Mrs Jacobs is enrolled for a MSc (Med) in Pharmacy at the University of Limpopo. Attached please find the proposal for the study entitled:” Initially prescribed antimicrobial treatment in an adult intensive care unit at Steve Biko Academic hospital as part of an Antimicrobial Stewardship roll out programme.”

The study has been approved by Prof A Stoltz who will also co-supervise the study. The proposal was submitted to the School of Health Care Sciences and the Medunsa Research and Ethics Committee at the University of Limpopo (Medunsa Campus). (Clearance Certificate: Project No: XXXXXX). The proposal will also be submitted to the University of Pretoria’s ethics Committee for approval.

The aim of the study is:

To investigate the initial use of antimicrobials as prescribed in an adult intensive care unit at Steve Biko Academic Hospital focussing on:

- Indication
- Duration of use
The objectives are:

- To identify which antimicrobials are initially prescribed for an adult intensive care unit.
- To determine if antimicrobials are prescribed appropriately according to patient diagnosis, weight, renal (urea and creatinine using Cockcroft and Gault) and hepatic markers (ALT, AST, GGT, Alk Phos, LDH, Total Bili and Direct Bili) as compared to the Standard Treatment Guidelines
- To investigate the use of antimicrobials against infection biomarkers (WBS count, CRP, temperature, blood culture, procalcitonin.) considering indication, dose and duration of treatment as compared to the Standard Treatment Guidelines
- To determine the direct costs associated with the initially prescribed antimicrobial therapy for a patient in a medical adult intensive care unit using daily defined dose.

Kindest regards,

Ms RC Jacobs

Researcher

Cc Dr N Schellack, Prof AGS Gous; Prof A Scholtz
APPENDIX 5: AUTHOR GUIDELINES

Manuscripts submitted to the SAJID must be in the form of Research Articles, Brief Reports, Clinical Case Studies, Correspondence, Reviews, State-of-the-Art Articles, Commentaries and Opinion Papers, Editorials or Supplement Articles. The Journal welcomes the publication of Guidelines, Conference Proceedings Newsletters or Press Releases, and Book Reviews. Articles, Brief reports and Reviews are peer reviewed; other categories are reviewed by the Editors. Commentaries and Editorials are generally invited contributions, indicating the authors’ identity, while manuscripts in the form of Reviews, and State-of-the-Art Articles may also be requested by the Editors.

All manuscripts must have conflict of interest and funding statements. When authors submit a manuscript, whether an article or a letter, they are responsible for disclosing all financial and personal relationships that might bias their work. To prevent ambiguity, authors must state explicitly whether potential conflicts do or do not exist. Authors should do so in the manuscript on a conflict-of-interest notification page that follows the title page.

Manuscripts describing research in human subjects or animals must indicate ethics clearance from appropriate research review committees. When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

Articles describe original investigations at an acceptable degree of completion, constituting an advance in the field. Articles must not exceed 3500 words of text, without counting the abstract, references or legends, and illustrations and tables must be limited to the minimum necessary for clear and concise presentation. The abstract
must either be structured, using *Background, Methods, Results, and Conclusions* as headings and comprising no more than 250 words, or unstructured with a 200 word limit. Articles are limited to a maximum of 7 insets (tables and figures combined) and 50 references.

**Reviewers**

The Journal would encourage authors to supply the names of at least 2 potential reviewers for their manuscript, as well as to indicate any reviewers they would feel may have a potential conflict of interest with regard to their submission.

**Supplements**

Requirements for supplement manuscripts generally follow those for SAJID manuscripts, including conflict of interest and funding statements. Inquiries relating to suitability of topic, programme organisation, production and costs should be made to the Editor.

**Evaluation of manuscripts**

*Review procedure.* The Editor-in-Chief and Emeritus Editor screen all unsolicited manuscript submissions and some of these are rejected without further review. All other manuscripts are sent to a minimum of two outside experts for review. After receipt of the reviewers’ reports, the Editor-in-Chief and the Emeritus Editor with administrative assistance of the Journal Secretary discuss the merits of the manuscripts and the Editor-in-Chief makes the final decision to accept, reject, or request revision of the manuscript. A request for revision does not guarantee ultimate acceptance of the revised manuscript.

*Related manuscripts.* If there appears to be significant overlap between a manuscript submitted to SAJID and another submitted manuscript by the same authors to SAJID or another journal, the editors will take the matter up with the corresponding author, and based on the response, take appropriate action (ask for modification, or reject with detailed explanation). Further action may include informing the appropriate authority in the authors’ resident institution and if overlapping is discovered after
publication in SAJID, publishing an appropriate announcement to that effect in the journal.

DOCUMENT REQUIREMENTS

Checklist

The following are required for your manuscript to be processed:

- Covering letter
- Word count limits
- Conflict of interest statement
- Funding statement
- List of potential reviewers

Covering Letter

All manuscripts submitted to SAJID must be accompanied by a letter declaring that the manuscript has not been submitted or accepted for publication elsewhere. This letter must confirm and declare that all authors have seen and approved the content and have contributed significantly to the work. Authors should suggest potential unbiased reviewers who are qualified to review their manuscript. A covering letter must also accompany a revised submission and must address issues raised in the review process.
Manuscript Preparation

The SAJID complies with the Uniform Requirements for Manuscripts Submitted to Biomedical Journal Journals (Ann Intern Med 2000; 133:229-231 [editorial]; http://www.icmje.org, full text). Text, tables, references, and legends must be double-spaced. Italicics should be used for genus and species names and for genes but not for in vivo, in vitro, in situ, et al., or other Latin-derived expressions. For layout of manuscript and appropriate style see a recent issue of SAJID.

Title page. On the title page, please supply a running head of not more than 40 characters and spaces, a title of not more than 160 characters and spaces, the names and affiliations of all the authors, and word counts of the abstract and text. Each author’s first name, subsequent initials and surname must be used.

Footnote page. Footnotes must include:

- Statement that authors either have or have not a commercial or other association that might pose a conflict of interest (e.g. pharmaceutical stock ownership, consultancy, advisory board membership, relevant patents, or research funding)
- Statement naming sources of financial support (including grant numbers)
- Name, date (month and year), and location (city, and country if not South Africa) of a meeting at which all or part of the information has been presented (include an abstract number, if available)
- Name, address, telephone and fax numbers, and e-mail address of the person to whom correspondence should be addressed
- Current affiliations and addresses for authors whose affiliations have changed since completion of the study

Abstract. The abstract for an Article may be structured with the headings Background, Methods, Results, and Conclusions (250-word limit) or unstructured (200-word limit). Abstracts of Brief Reports should be no more than 100 words. Whether structured or unstructured, the abstract must state the purpose of the
research, the methods used, the results, and the conclusions. Do not cite references in the abstract. Include up to 10 key words, separate from the abstract. Please remember that the abstract is particularly useful for literature retrieval purposes.

Text. The text of Articles must be no longer than 3500 words, and that of Brief Reports no longer than 2000 words. The Methods section must include a statement that informed consent was obtained from patients or their parents or guardians, and human experimentation guidelines of the National Department of Health (http://www.doh.gov.za) or the South African Medical Research Council (MRC; http://www.sahealthinfo.org/ethics/index.htm) and/or those of the authors’ institution(s) were followed in the conduct of clinical research or that animal experimentation guidelines (see MRC website above) were followed in animal studies.

References. Articles are generally limited to 50 references, Brief Reports to 15 references. Only works that have been published or accepted for publication can be included in the reference list. Unpublished observations by the authors (authors’ unpublished data) personal communications (SP Stanley, personal communication), and manuscripts submitted for publication (J Odendaal, S Coovadia and J Radebe, submitted) should be mentioned parenthetically in the text Please number references in order of appearance; those cited only or first in tables or figures are numbered according to the order in which the table or figure is cited in the text. Example: If table 3 is cited in the text after reference 20, a new reference cited in table 3 will be reference 21.

References must follow the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org, full text). Provide all authors’ (or editors’) names when there are fewer than 7; for 7 or more, list the first 3 and add “et al.” Titles of journals not listed in Index Medicus should be spelt out in full. Reference to a doctoral thesis or Master’s dissertation should include the author, title, institution, location, year and publication information, if published. For online resources, include a URL and date accessed. Accuracy of references is the responsibility of the authors.

Examples of the proper format are as follows:


Acknowledgment(s). The page preceding the references may include a statement thanking those who assisted substantially with work relevant to the study.

Statistical analysis. The statistical analyses used should be identified both in the text and in all tables and figures where the results of statistical comparison are shown.

Units of measure. All Data should be expressed in metric units; use of SI units is encouraged. Use °C for temperature.

Tables and figures. Articles are limited to a maximum of seven inserts (tables and figures combined), Brief Reports to a maximum of two inserts. Data should not be repeated in both a table and a figure. Abbreviations and acronyms used in tables and figures must be explained in the table footnotes and figure legends, even if already defined in the text.

Tables should be numbered in the order of mention in the text. Tables should be typed double-spaced throughout, with no vertical or internal rules. Footnotes and accompanying explanatory material should be kept to a minimum. Footnotes should be placed below the table and designated by superscript lowercase letters (listed in order of location when the table is read horizontally). Each column must have an appropriate heading describing the data in the column below, and units of measure must be clearly indicated. For further instructions on the preparation of tables in Word, consult the Special Instructions for Tables.

Figures should be also numbered in the order of mention in the text and should appear at the end of the manuscript and references. Your figures should be prepared in accordance with the Guidelines for Submission of Artwork. Letters, numbers, and symbols should be clear and of sufficient size to be legible when the figures are reduced. Photomicrographs should have internal scale markers. Figures reproduced from other publications must be accompanied by permission from the copyright holder. If the manuscript is accepted, the author will be required to send one complete set of glossy, hard-copy figures.

Figure legends should be double-spaced and appear on a separate page preceding the figures. Any abbreviations or symbols used but not defined in the figure itself must be defined in the legend.


For commercially obtained products mentioned in the text, list the full names of manufacturers. Generic names of drugs and other chemical compounds should be used.
Nomenclature. SAJID recommends the latest widely accepted nomenclature, as set out in documents prepared by recognised international agencies e.g. the *International Journal of Systematic and Evolutionary Microbiology, Bergey’s Manual of Determinative Bacteriology* (9th ed., revised, Williams & Wilkins, 1993), *Virus Taxonomy – The Classification and Nomenclature of Viruses: Sixth Report of the International Committee on Taxonomy of Viruses* (Springer-Verlag, 1995). The latter document also supplies standard abbreviations for virus species.
APPENDIX 6: MEDUNSA RESEARCH AND ETHICS COMMITTEE CLEARANCE CERTIFICATE

UNIVERSITY OF LIMPOPO
Medunsa Campus

MEDUNSA RESEARCH & ETHICS COMMITTEE
CLEARANCE CERTIFICATE

MEETING: 87/2012
PROJECT NUMBER: MREC/H/212/2012: PG
PROJECT:
Title: Initial Antimicrobial use in Medical Adult Intensive Care Unit: Indication and Cost Analysis at Steve Biko Academic Hospital, Pretoria

Researcher: Miss R Jacobs
Supervisor: Dr N Schellack
Co-supervisor: Prof AGS Gous
Prof A Stoltz
Hospital Superintendent: Dr BJ Ribeiro (Steve Biko Academic Hospital)
Department: Pharmacy
School: Health Care Sciences
Degree: MSc Pharmacy

DECISION OF THE COMMITTEE:
MREC approved the project.

DATE: 12 September 2012

[Signature]
PROF GA OGUNBANJO
CHAIRPERSON MREC

The Medunsa Research Ethics Committee (MREC) for Health Research is registered with the US Department of Health and Human Services as an International Organisation (IRCR0004319), as an Institutional Review Board (IRB00005122), and functions under a Federal Wide Assurance (FWA00009419).
Expiry date: 11 October 2016

Note:
i) Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee.

ii) The budget for the research will be considered separately from the protocol. PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.
APPENDIX 7: UNIVERSITY OF PRETORIA AND ETHICS COMMITTEE CLEARANCE CERTIFICATE

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

* IRB 0000 2235 IORG0001762 Approved dd 13/04/2011 and Expires 13/04/2014.

DATE: 1/10/2012

<table>
<thead>
<tr>
<th>NUMBER</th>
<th>178/2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE OF THE PROTOCOL</td>
<td>Initially prescribed antimicrobial treatment in a medical adult intensive care unit at Steve Biko Academic hospital as part of an Antimicrobial Stewardship roll out programme.</td>
</tr>
</tbody>
</table>
| PRINCIPAL INVESTIGATOR | Student Name & Surname: Miss Regina Catharina Jacobs
Dept: Steve Biko Academic Hospital, University of Pretoria.
Student of University of Limpopo
Cell: 0845135120 E-Mail: tarinarc@hotmail.com |
| SUPERVISOR (ONLY when STUDENT(S)) Name & Surname: Dr N Schellack E-Mail: nschellack@gmail.com |
| CO-SUPERVISOR | Prof AGS Gous – E-mail: andries.gous@gmail.com
Prof A Stoltz – E-mail: anton.stoltz@up.ac.za |
| STUDY DEGREE | MSc (Med) in Pharmacy |
| SPONSOR COMPANY | Not Applicable |
| CONTACT DETAILS OF SPONSOR | Not Applicable |
| SPONSORS POSTAL ADDRESS | |
| MEETING DATE | 26/09/2012 |

The Protocol and Informed Consent Document were approved on 26/09/2012 by a properly constituted meeting of the Ethics Committee subject to the following conditions:

1. The approval is valid for 1 years period [till the end of December 2013], and
2. The approval is conditional on the receipt of 6 monthly written Progress Reports, and
3. The approval is conditional on the research being conducted as stipulated by the details of the documents submitted to and approved by the Committee. In the event that a need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.
**Members of the Research Ethics Committee:**

<table>
<thead>
<tr>
<th>Name</th>
<th>Title and Qualification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof M J Bester</td>
<td>(female) BSc (Chemistry and Biochemistry); BSc (Hons)(Biochemistry); MSc(Biochemistry); PhD (Medical Biochemistry)</td>
</tr>
<tr>
<td>Prof R Delport</td>
<td>(female) BA et Sci, B Curationis (Hons) (Intensive care Nursing), M Sc (Physiology), PhD (Medicine), M Ed (Computer Assisted Education)</td>
</tr>
<tr>
<td>Dr NK Likibi</td>
<td>MBB HM – Representing Gauteng Department of Health MPH</td>
</tr>
<tr>
<td>Dr MP Mathebula</td>
<td>(female) Deputy CEO; Steve Biko Academic Hospital; MBCHB, PDM, HM</td>
</tr>
<tr>
<td>Prof A Nienaber</td>
<td>(female) BA(Hons)(Wits); LLB; LLM; LLD(UP); PhD; Dipl.Dataometrics(UNISA) – Legal advisor</td>
</tr>
<tr>
<td>Mrs MC Nzeku</td>
<td>(female) BSc(NUL); MSc(Biochem)(UCL, UK) – Community representative</td>
</tr>
<tr>
<td>Prof L M Ntlhe</td>
<td>MbChB (Natal) FCS (SA)</td>
</tr>
<tr>
<td>Snr Sr J Phatoli</td>
<td>(female) BCur(Eet.A); BTEc(Oncology Nursing Science) – Nursing representative</td>
</tr>
<tr>
<td>Dr R Reyniers</td>
<td>MBChB (Prêt), FCPaed (CMSA) MRCPCH (Lon) Cert Med. Onc (CMSA)</td>
</tr>
<tr>
<td>Dr T Rossouw</td>
<td>(female) MBChB (cum laude); M.Phil (Applied Ethics) (cum laude), MPH (Biostatistics and Epidemiology (cum laude), D.Phil</td>
</tr>
<tr>
<td>Dr L Schoeman</td>
<td>(female) B.Pharm, BA(Hons)(Psych), PhD – Chairperson: Subcommittee for students’ research</td>
</tr>
<tr>
<td>Mr Y Sikweyiya</td>
<td>MPH; SARETI Fellowship in Research Ethics; SARETI ERCTP; BSc(Health Promotion)Postgraduate Dip (Health Promotion) – Community representative</td>
</tr>
<tr>
<td>Dr R Sommers</td>
<td>(female) MBChB; MMed(Int); MPharmMed – <strong>Deputy Chairperson</strong></td>
</tr>
<tr>
<td>Prof TJP Swart</td>
<td>BChD, MSc (Odont), MChD (Oral Path), PGCHE – School of Dentistry representative</td>
</tr>
<tr>
<td>Prof C W van Staden</td>
<td>MBChB; MMed (Psych); MD; FCPsych; FTCL; UPLM – <strong>Chairperson</strong></td>
</tr>
</tbody>
</table>

**DR R SOMMERS;** MBChB; MMed(Int); MPharmMed.
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

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